World Health Organization

WHO R&D Blueprint

COVID-19

Informal consultation on the role of therapeutics in COVID 19 prophylaxis and post-exposure prophylaxis.

WHO reference number

Geneva, Switzerland, 18th March 2020

R&DBlueprint

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Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

Currently, there are no licensed vaccines for the prevention of COVID 19. While efforts continue to develop efficacious vaccines, it is pertinent to examine the possible role of therapeutic agents in protecting healthcare workers and the general populace who are at significant risk of contracting the virus, either before they are exposed to the virus or to prevent the development of clinical disease following exposure.

This expert consultation convened clinical care partners and experts in the field of randomized controlled trials (RCTs), biostatistics, regulatory affairs, preclinical studies, and pharmacology to evaluate current progress in the area of COVID 19 chemoprophylaxis.

OBJECTIVES OF THE CONSULTATION

The objectives of this consultation were:

1. To review and critically appraise the existing evidence regarding promising therapeutics for chemoprophylaxis.

2. To decide on the best approach to evaluate the prophylactic and post-exposure prophylactic efficacy of the highlighted therapeutics.

This Consultation represents an initial step towards the evaluation of available evidence and harmonization of ongoing scientific efforts.

Agenda items

- Introduction and roll-call.
- Update on current plans and protocols for prophylaxis.
- Conclusions and next steps.

Participants

Chair: Marco Cavaleri

Name	Position	Institutional Affiliation
Marco Cavaleri	Head of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Eric Pelfrene	Office of Anti-infectives and Vaccines	European Medicines Agency, Netherlands
Sina Bavari	Independent Consultant	
Karl Erlandson	Interdisciplinary Scientist	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Yaseen Arabi	Chairman, Intensive Care Department	King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Name	Position	Institutional Affiliation
John Marshall	Co-Director, Critical Illness and Injury Research Centre, St Michael Hospital, Canada	Co-Director, Critical Illness Research, St Michaels Hospital
Ross Upshur	Director, Primary Care Research Unit, Sunnybrook and Women's College Health Sciences Centre, Canada Research Chair in Primary Care Research	University of Toronto, Canada
John Beigel	Associate Director for Clinical Research	NIH, USA
Thomas Fleming	Professor of Biostatistics	University of Washington
John Farley	Director, Office of Infectious Diseases	FDA, USA
Philip Krause	Deputy Director CBER/OVRR	FDA, USA
Peter Dull	Deputy Director, Integrated Clinical Vaccine Development	Bill & Melinda Gates Foundation, USA
Ken Duncan	Discovery & Translational Sciences team Lead	Bill & Melinda Gates Foundation, USA
Nicholas White	Professor of Tropical Medicine	Mahidol University, Thailand
Robert Walker	Chief Medical Officer and Director, Division of Clinical Development	Biomedical Advanced Research and Development Authority, US Department of Health and Human Services
Julia Tree	Microbiological Services	Public Health England

Name	Position	Institutional Affiliation
Scott Miller	Deputy Director, medical interventions	Bill & Melinda Gates Foundation, USA
Frederick Hayden	Professor Emeritus, Medicine: Infectious Diseases and International Health	University of Virginia
Jacqueline Kirchner	Senior Program Officer	Bill & Melinda Gates Foundation, USA
Elizabeth Higgs	Global health science advisor for the Division of Clinical Research (DCR)	NIH. USA
Helen Rees	Professor, Wits Reproductive Health and HIV Institute	University of Witwatersrand, South Africa
White	Associate Professor, Microbiology and Immunology	University of Maryland School of Medicine
Oriol Mitjà	Associate Professor, Infectious Diseases	Universitari Germans Trias I Pujol, Barcelona
Ruanne Barnabas	Associate Professor in Global Health and Medicine	University of Washington
Michael Avidan	Professor of Anaesthesiology	Washington University, St Loius

Other invited experts but only those listed in the table above participated: Hilary Marston (US NIH), Philip Coyne (US PHS), Sina Bavari (Independent consultant), Jeremy Farrar (Wellcome Trust, UK), Markus Mueller (University of Wien), Bin Du (Peking), Yi Guan (Hong Kong); Wannian Liang (MOH China), Bruno Lina (France), Claire Madelaine William Dowling (CEPI, USA) David R Boulware(Minnesota, USA).

WHO Secretariat: Alejandro Costa, Janet Diaz, Ana Maria Henao-Restrepo, Marie-Pierre Preziosi, Ximena Riveros Balta, Kolawole Salami, Emer Cooke, Deusdedit Mubangizi, and Pierre Gsell. David Schellenberg, Pascal Ringwald.

OVERVIEW OF THE DELIBERATIONS

Overall considerations

- The WHO preliminary considerations on a generic protocol was provided for the scientific evaluation of chemoprophylaxis in both pre and post exposure prophylaxis scenarios. A double blind randomized placebo-controlled clinical trial is the encouraged methodology. Randomization could either be at the individual or household clusters or rings around an index case. However, randomization within units is preferable to between units if the aim is to assess effect of prophylaxis on transmission. Protection against illness and infection can, however, be assessed in both individual or cluster randomization; with 'herd protection' assessment more feasible in cluster randomization.

- The Barcelona PEP study is in collaboration with the department of health. It is pertinent as there are currently more than 10,000 confirmed cases of COVID 19 in Spain, and the daily count is progressively increasing with an average R_0 of 3. The aim is to evaluate the efficacy of antiviral treatment in reducing transmission (measured as secondary attack rate) and disease progression in individuals who are found to be infected and their contacts through chemoprophylaxis. The sample size was calculated as 190 non-severe cases of PCR confirmed COVID 19 with a defined ring of 15 contacts around a case translating to an estimated 3,000 contacts. Randomization was 1:1 at the ring level. The power was calculated to detect a 10% difference in incidence of secondary cases among contacts, i.e. expecting15% incidence in control arm, and 5% in intervention arm. The confirmed cases in the intervention arm will offered antiviral treatment darunavir 800 mg / cobicistat 150 mg tablets (oral, 1 tablet q24h, taking for 7 days) and Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 6 days [OHCQ 800mg d1, 400mg d2-4 (total dose 2,0g)]), while their contacts would receive hydroxychloroquine

(800 mg loading dose on day one, followed by 400mg daily for six days, giving a total of 3.2 g). The control arm would receive local standard of care, i.e., home isolation for the contacts and supportive care for the cases. Primary outcomes are the rate of PCR positivity and development of symptoms in the contacts and measurement of transmissibility through repeated throat swabs + PCR or the measurement of IgM and IgG. The study has already commenced with 12 patients recruited already. The results are expected in 3 weeks.

- The Mahidol Oxford Research Unit coordinates the PrEP Study in Southeast Asia. It is planned as a multicentre study involving Thailand, Vietnam, Laos, India, Myanmar, and Cambodia, but will also be conducted in Europe with hydroxychloroquine. The study aims to determine if chloroquine prophylaxis attenuates disease in confirmed cases and prevents symptomatic COVID 19 infection in healthcare workers or other groups at high risk. It's a double-blind placebo-controlled clinical trial of 40,000 adult subjects at high-risk of COVID 19 who would be randomized 1:1 into either an intervention group that would receive a loading dose of 10mg/kg body weight chloroquine, followed by a daily dose of 155mg for 3 months or until they are diagnosed with COVID 19; or a control group that would receive a placebo. The primary outcome measures are PCR confirmed COVID 19 cases and severity score. Prophylaxis will continue for 3 months. The challenges anticipated include rapidity of the ethics and regulatory reviews and approval processes. In order to overcome potential hurdles related to acceptance of product not approved in Europe, the team is considering a UK company as an alternative to sidestep this challenge (hydroxychloroquine has been included).

- The University of Washington/BMGF study aims to determine the efficacy of hydroxychloroquine to prevent SARS-CoV-2 infection among close adult contacts of confirmed COVID-19 cases. The study would randomize by household 2,000 healthy adults without any symptoms of COVID 19, but with contact with a confirmed case in the last 4 days, into an intervention arm that would receive hydroxychloroquine 400mg twice daily for 3 days followed by 200mg once daily for 11 days; or a control arm that would receive low dose vitamin C for 14 days. Daily mid-nasal swabs are self-collected daily for 14 days

and 1 week later; samples are then shipped to be tested. The outcomes of the study are PCR confirmed COVID-19(primary) and disease severity (secondary). The study is planned to take place entirely remotely. There are plans to increase the sample size if the attack rate is lower than the estimated 6% used for sample size calculation and to increase the power of the study in case the effect of the intervention is lower than expected.

- There is another study ongoing from the University of Minnesota in Health Care workers. They were not present, but they sent the slides. The study aims to test if post-exposure prophylaxis with hydroxychloroquine can prevent the progressive development of symptomatic COVID19 disease after known exposure to the SARS-CoV2 virus. 1,500 healthcare workers and adult household contacts who have been exposed to COVID 19 within the past three days would be randomized 1:1 into an intervention arm that receives hydroxychloroquine, 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600mg once a day for 6 consecutive days, or a control group that would receive placebo. The primary outcome measure is the number of participants at 14 days post-enrolment progressed to symptomatic active COVID19 disease (severity score self-reported).

- The choice of the endpoint for the clinical studies was discussed. Whether prevention of disease of any severity can be seen as adequate or considering severity of disease should be preferred is still a matter of debate. Some experts were of the opinion that a mild or asymptomatic infection could lead to the development of desirable long-lasting immunity and it might not be ideal to have this an outcome in a PrEP or PEP study. The Impact of prophylaxis on transmission and ensuring the development of protective immunity for healthcare workers are considered relevant outcomes. At the same time, preventing severe disease (requiring hospitalization) is also of major importance. Prevention of infection is also relevant from a transmission perspective and will be investigated in the University of Washington study among others.

- Most of the studies are excluding children as very little information of COVID 19 in children is currently available, including a good understanding of their

role in the transmission of the virus. It is however noted that children can be infected and therefore could be in principle considered. The benefit risk balance in children of drugs to be tested needs also to be considered. the team in Barcelona is aiming to include paediatric subjects in their study and would be willing to share their plans with other teams.

- It was observed the large variability in dosage, target population and trial design. WHO is working on a core protocol that could be ideally implemented in several countries with the main objective to protect Health Care Workers and limit the nosocomial transmission.

CONCLUSIONS & PROPOSED NEXT STEPS:

- Post-exposure prophylaxis (PEP) is intended for:

- health care workers with a documented unprotected exposure, either due to ineffective triage of a suspect case or lack of proper PPE.

- It is also a strategy to be investigated for household contacts of an index case in a home setting to prevent the spread (most of the community transmission appears to be linked to household contacts). It requires adequate dosing to achieve protective drug levels based on current estimates from in vitro activity, and sustained dosing through the incubation period of 14 days.

- Pre-exposure prophylaxis (PrEP) is intended primarily for health care workers likely to be exposed if PPE is not likely available or inadequate for protection. As administration is going to be continued for likely long periods of potential exposure (studies are targeting 90 days), long-term tolerability of investigated drugs is of primary importance (.

- The supply chain of chloroquine needs to be given better attention as the scale-up in their use for experimental purposes in COVID 19 continues.

Countries may have already banned exportation of the commodity among other measures. The WHO malaria team will examine the supply chain of chloroquine to ensure that countries still using it for malaria response would not have their supply compromised, especially as the API for chloroquine comes mainly from China. David Reddy of Medicines for Malaria Venture has extensively mapped out API, raw materials, and manufacturing capacity globally. WHO team to reach out to David Reddy. Nick White is also supporting the WHO in this aspect.

- The level of CQ/HCQ free drug in the pulmonary epithelial cells is unknown, and in the absence of animal models, it Is difficult to conclude whether either drugs will be able to exert effective antiviral activity in humans. Further evidence from animal models or studies in humans of ELF penetration could inform dose selection. . The different doses and posology proposed should be reconciled as much as possible in light of the available pharmacokinetics and safety knowledge.

- WHO expert group has already developed a draft prophylaxis protocol.

- WHO will convene another meeting to further deliberate on endpoints, the most ideal dose of chloroquine for the studies, and harmonization of protocols.

- WHO will share the report of chloroquine landscape analysis prepared by Prof. Nick While with group members ahead of the next meeting.

- All partners that are planning or have started a clinical trial should share their protocols with WHO

Note that the above prioritization decisions are preliminary and may change as further information is provided to WHO.